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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,628	04/04/2007	Christian Peter Petzelt	02839/46201	8178

26646 7590 06/18/2010

KENYON & KENYON LLP
ONE BROADWAY
NEW YORK, NY 10004

EXAMINER	
ARNOLD, ERNST V	
ART UNIT	PAPER NUMBER
1616	
MAIL DATE	DELIVERY MODE
06/18/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,628	PETZELT ET AL.	
	Examiner	Art Unit	
	ERNST V. ARNOLD	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-14 and 20-24 have been cancelled. Claims 15-19 are under examination.

Withdrawn rejections:

Applicant's amendments and arguments filed 6/14/10 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed below is herein withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-19 remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention without an undue amount of experimentation.

Let the Examiner be clear: Applicant is not enabled for *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture.*

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: 1) scope or breadth of the claims; 2) nature of the invention; 3) relative level of skill possessed by one of ordinary skill in the art; 4) state of, or the amount of knowledge in, the prior art; 5) level or degree of predictability, or a lack thereof, in the art; 6) amount of guidance or direction provided by the inventor; 7) presence or absence of working examples; and 8) quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure. When the above factors are weighed, it is the Examiner's position that one skilled in the art could not practice the invention without undue experimentation. While all of the factors have been considered, only those required for a *prima facie* case are set forth below.

1) Scope or breadth of the claims

2) Nature of the invention

The nature of the invention is directed to *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a*

human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture.

3) Relative level of skill possessed by one of ordinary skill in the art

MPEP 2141.03 states (in part), "A person of ordinary skill in the art is also a person of ordinary creativity, not an automaton." KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727, 167 LEd2d 705, 82 USPQ2d 1385, 1397 (2007). "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." Id. Office personnel may also take into account "the inferences and creative steps that a person of ordinary skill in the art would employ." Id. At 1396, 82 USPQ2d at 1396. The "hypothetical person having ordinary skill in the art' to which the claimed subject matter pertains would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art." Ex parte Hiyamizu, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (The Board disagreed with the examiner's definition of one of ordinary skill in the art (a doctorate level engineer or scientist working at least 40 hours per week in semiconductor research or development), finding that the hypothetical person is not definable by way of credentials, and that the evidence in the application did not support the conclusion that such a person would require a doctorate or equivalent knowledge in science or engineering.).

4) State of, or the amount of knowledge in, the prior art

The sourcebook of models for biomedical research directs one of ordinary skill in the art to the use of animal models in sepsis (pages 473 and 474 of: Sourcebook of

Models for Biomedical Research Humana Press; P.Michael Conn Ed.; 2008 New Jersey).

Weber et al. teach that: "In the CLP model signs of apoptosis could be found in thymus, lung and intestinal mucosa and epithelium." (Page 120 of: Cell Apoptosis Research Progress 2008; Robert H. Fenton and Calvin V. Burnside Eds; Nova Science Publishers, Inc., NY). *Note that the endothelium was not included.*

5) Level or degree of predictability, or a lack thereof, in the art

In an animal model of sepsis, Hotchkiss found no evidence of endothelial cell apoptosis in the aorta (Hotchkiss; middle column of page S227 of: Crit Care Med 2002, 30(5), S225-S228). Hotchkiss also report on the different observations of *in vitro* systems that results in contradictory results (page S227, left column). Hotchkiss discloses that: "The role of endothelial cell apoptosis in sepsis remains inconclusive." (page S227, summary). Furthermore, "it is possible that endothelial cell apoptosis may either be beneficial or detrimental to the host." (page S228, left column). The Examiner notes that endothelial cells line the vasculature and are not limited to just the intestine.

Winn et al. (Journal of Thrombosis and haemostasis 2005, 3, 1815-1824) teach: "whether endothelial cell apoptosis occurs in sepsis is somewhat controversial." (page 1819, left column, sepsis).

"Since *in vitro* cell culture models cannot account for "unknown" mechanisms of action, which are detected in live animals (where all the relevant interactions occur), the predictive value of non-animal alternative tests is limited at present." (page 482 of: Risk

Assessment of Chemicals: An Introduction Second Edition; C.J. van Leeuwen and T.G. Vermeire Eds. 2007, Springer; Dordrecht, The Netherlands).

Frantz (Nature Reviews Drug Discovery; 2003, 2, page 501) teaches that the use of cell culture and recombinant human cells provide valuable alternatives to animal experiments but these studies still cannot predict the integrated response of a potential drug as accurately as living systems in which a combination of genetic, biochemical, physiological, pathological and environmental influences work in concert (left column).

Anderson et al. (page 743 of: Journal of Antimicrobial Chemotherapy 2008, 62, 738-745) comments on in vitro studies: "…given the exploratory nature of the study, all findings should be considered to be hypothesis generating. Further confirmatory research is needed to understand the mechanisms." And; "…and taken together, our findings provide scientific direction for future research in this area. ***Lastly, as in all in vitro research, we cannot predict how our findings translate into patients.*** The *in vivo* system is many times more complex than *in vitro* conditions…". (Examiner added emphasis).

6) Amount of guidance or direction provided by the inventor

Applicant was required to provide in the specification additional guidance and direction with respect to how use the claimed subject matter in order for the application to be enabled with respect to the full scope of the claimed invention. Although the instant specification discloses that *in vitro* assays of LDH production from cortical neurons and HeLa cells and *in vitro* suppression of caspase 3/7 (Figures 1, 2 and 4 for example), it remains silent on *a method of reducing apoptotic cell death in endothelial*

cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture. There exists a vacuum of information between the *in vitro* data taught by Applicant and actually reducing apoptosis in endothelial cells in the intestine in sepsis. The critical teaching that ties the *in vitro* data to intestinal endothelial cell apoptosis in sepsis is missing. Applicant is merely guessing that their *in vitro* data could be extrapolated to a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis without actually showing anything. In other words, *in vitro* methods can be used to generate ideas and develop hypotheses but cannot be used alone for making broad sweeping assertions about how the *in vitro* results might work in a complex biological system let alone a biological system that is further complicated by a pathological condition (sepsis).

7) Presence or absence of working examples

The specification fails to provide scientific data and working embodiments with respect to *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture*. Applicant performed some *in vitro* tests on cortical neurons and HeLa cells in examples 1-4 but not with endothelial cells. ***None of the examples were models for apoptosis in sepsis***. Applicant merely has a general idea and is assuming that their *in vitro* data can be correlated with reducing endothelial cell apoptosis in the intestine in sepsis. There is

no objective evidence that provides the link from Applicant's *in vitro* data to a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis.

8) Quantity of experimentation required to make and use the claimed invention based upon the content of the supporting disclosure

All Applicant has is a general idea based upon some *in vitro* data with only the intimation that *a method of reducing apoptotic cell death in endothelial cells of the intestine in sepsis comprising administering to said a human an effective amount of a pharmaceutical preparation comprising xenon or a xenon gas mixture* can work. Applicant has not shown any data concerning endothelial cell apoptosis and expects a leap of faith without providing a bridge of logic that the instant method would have any reduction of endothelial apoptotic cell death in sepsis. This is especially true when the art, Hotchkiss, whom actually performed experiments on an animal model of sepsis in contrast to Applicant, and did not find any sign of endothelial cell apoptosis in the aorta and the art. The art is not even sure if endothelial cells undergo apoptosis during sepsis! How is the method supposed to work when it is not yet certain that endothelial cells undergo apoptosis in sepsis? In other words, there is no method if the endothelial cells do not undergo apoptosis in sepsis. Furthermore, Anderson et al. teach how *in vitro* testing cannot predict responses *in vivo*. For all intents and purposes, Applicant has left it to one of ordinary skill in the art to figure out if endothelial cells undergo apoptosis in sepsis and if xenon will have any effect in reducing that. Essentially, the artisan has to figure out how to do this themselves. As a result, one of ordinary skill in the art would be

required to conduct an undue amount of experimentation to determine if endothelial cells have reduced apoptosis in the intestine in sepsis in the method instantly claimed.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (Genentech, Inc. v. Novo Nordisk, A/S, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997)).

The enablement requirement is not satisfied.

Response to Arguments:

Applicant asserts that the Examiner is incorrect in interpreting the publication (Conn) referred to in the quote above (see remarks page 2). Applicant asserts that the publications cited cannot support the enablement rejection because both publications are directed to areas that have nothing to do with sepsis (see remarks page 3). Applicant further argues that "the enablement requirement obligates the applicant to teach those skilled in the art how to practice the claimed invention without undue experimentation." And on page 5 of remarks, "much of the argument provided in the Office Action to support this rejection appears to be concerned with questions of utility, i.e., whether the invention will work." Respectfully, the Examiner cannot agree and will address these points in turn.

Respectfully, Applicant's argument that that the Examiner is incorrect in interpreting the publication (Conn) and that the publications are directed to areas that have nothing to do with sepsis is not persuasive. The Examiner has very carefully

woven unpredictability in the sepsis art by drawing in the references of Hotchkiss and Winn who teach: “Hotchkiss discloses that: “The role of endothelial cell apoptosis in sepsis remains inconclusive.” (page S227, summary). Furthermore, “it is possible that endothelial cell apoptosis may either be beneficial or detrimental to the host.” (page S228, left column). The Examiner notes that endothelial cells line the vasculature and are not limited to just the intestine. Winn et al. (Journal of Thrombosis and haemostasis 2005, 3, 1815-1824) teach: “whether endothelial cell apoptosis occurs in sepsis is somewhat controversial.” (page 1819, left column, sepsis).” Applicant has not argued the position of the Examiner that endothelial cell apoptosis in sepsis remains inconclusive/controversial. Furthermore, Anderson et al. teaches as a general state of the art that “as in all *in vitro* research, we cannot predict how our finding translate into patients.” It remains the Examiner's position that "all *in vitro* research" includes sepsis research.

Respectfully, Applicant’s arguments that: “the enablement requirement obligates the applicant to teach those skilled in the art how to practice the claimed invention without undue experimentation.”; and, “much of the argument provided in the Office Action to support this rejection appears to be concerned with questions of utility, i.e., whether the invention will work.”; are not persuasive. First of all, utility is an issue under 35 USC 101 and in the instant case there is a practical utility of treating sepsis. It is the position of the Examiner that the instant claims are not enabled. From MPEP 2164.01: " Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained

sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention." And: "Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988)." And: "Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984)." The Examiner has properly made a proper factual determination that one of ordinary skill in the art cannot make or use this invention. The Examiner raised these questions which were not answered by Applicant: "The art is not even sure if endothelial cells undergo apoptosis during sepsis! How is the method supposed to work when it is not yet certain that endothelial cells undergo apoptosis in sepsis? In other words, there is no method if the endothelial cells do not undergo apoptosis in sepsis."

Finally, although the reference of Finley has not been applied Applicant argues that the dose of xenon used in Finely is several orders of magnitude below the dose that could cause any known physiological effects and there is no mention of the use of xenon to treat sepsis. The Examiner points out that instant claim 15 comprises any amount of xenon and it is merely applicants opinion that no physiological effects are performed. It only requires xenon to interact with one biological molecule to make a physiological effect as the xenon has affected the biomolecule.

Respectfully, this is a classic example of Applicant having a respectable guess that some *in vitro* data could be extrapolated to a method of reducing apoptotic cell death in endothelial cells in sepsis. The relevant case law states: In *In re '318 Patent Infringement Litigation*, 92 USPQ2d 1385 (Fed. Cir. 2009) at 1391, 1392 the court stated, "Thus, at the end of the day, the specification, even read in light of the knowledge of those skilled in the art, does no more than state a hypothesis and propose testing to determine the accuracy of that hypothesis. That is not sufficient. See *Rasmusson V. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005) ("If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis.")".

Applicant's arguments are not persuasive and the claims remain rejected.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ERNST V. ARNOLD whose telephone number is (571)272-8509. The examiner can normally be reached on M-F 7:15-4:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on 571-272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ernst V Arnold/
Primary Examiner, Art Unit 1616